

Form PTO 1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 5-93)		ATTORNEY'S DOCKET NUMBER P50869
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/889904
INTERNATIONAL APPLICATION NO. PCT/US00/01956	INTERNATIONAL FILING DATE 25 January 2000	PRIORITY DATE CLAIMED 25 January 1999
TITLE OF INVENTION ANTI-ANDROGENS AND METHODS FOR TREATING DISEASE		
APPLICANT(S) FOR DO/EO/US Dennis J. MURPHY, Patrick J. WIER, and Giuseppe Arnaldo Maria GIARDINA		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☒ Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/US00/01956, filed 25 January, 2000, which claims benefit from Provisional Application Serial No. 60/117,059, filed 25 January 1999.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ An Abstract on a separate sheet of paper.
19. ☐ Other items or information:

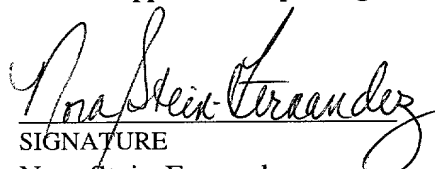
09889904-091001

US APPLICATION NO. (if known see 37 CFR 1.50) 09/889904		INTERNATIONAL APPLICATION NO. PCT/US00/01956		ATTORNEYS DOCKET NO. P50869	
20. [X] The following fees are submitted:				CALCULATIONS PTO USE ONLY	
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):				\$690.00	
Search Report has been prepared by the EPO or JPO\$860.00					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482)\$690.00					
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))\$710.00					
Neither International Preliminary Examination Fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$1,000.00					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$100.00					
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$690.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$0.00	
Claims	Number Filed	Number Extra	Rate		
Total claims	8 - 20 =	0	0 x \$18.00	\$0.00	
Independent claims	3 - 3 =	0	0 x \$80.00	\$0.00	
Multiple dependent claims (if applicable)			+ \$270.00	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$690.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
SUBTOTAL =				\$690.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				\$	
TOTAL NATIONAL FEE =				\$690.00	
				Amount to be refunded	\$
				charged	\$ 690.00

- a. ☐ A check in the amount of \$_____ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **\$690.00** to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570. A duplicate copy of this sheet is enclosed.
- d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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Attorney Docket No: P50869

IN THE UNITED STATES INTERNATIONAL EXAMINING AUTHORITY

International Application No.: PCT/US00/01956
International Filing Date: 25 January 2000
Priority Date Claimed: 25 January 1999
Applicant for DO/US: Murphy et al.
Title of Invention: ANTI-ANDROGENS AND METHODS
FOR TREATING DISEASE

Assistant Commissioner of Patents
Box PCT
Washington D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Preliminary to calculating filing fees and examining this application,
please amend the application as follows.

IN THE CLAIMS:

Please amend claim 5, as follows:

5. (Amended) The method according to claim 1 wherein the
compound is a neurokinin-3 receptor antagonist.

Please add new claims 7 and 8, as follows:

--7. The method according to claim 3 wherein the compound is a
neurokinin-3 receptor antagonist.

8. The method according to claim 4 wherein the compound is a
neurokinin-3 receptor antagonist.--

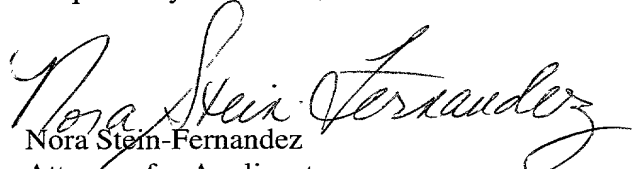
REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/US00/01956 into the U.S. national phase of prosecution. Claim 5 has been amended so that it complies with proper U.S. claim format. Claims 7 and 8 have been added and are directed to specific embodiments of this invention supported in the specification and claims as originally filed. An Abstract has been included on a separate page.

In view of the foregoing, favorable consideration of amended claim 5 and new claims 7 and 8, early examination on the merits and allowance of this application with are respectfully solicited.

A Version with Markings to Show Changes Made to the claims is attached.

Respectfully submitted,


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VERSION WITH MARKINGS TO SHOW CHANGES MADE

What is claimed is:

5. The method according to [claims 1, 3 and 4] claim 1 wherein the compound is a neurokinin-3 receptor antagonist.

7. The method according to claim 3 wherein the compound is a neurokinin-3 receptor antagonist.

8. The method according to claim 4 wherein the compounds is a neurokinin-3 receptor antagonist.

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FOOTED-4068880

ANTI-ANDROGENS AND METHODS FOR TREATING DISEASEFIELD OF THE INVENTION:

This invention relates to a method of treatment and/or prophylaxis of diseases, in a mammal, for which gonadotropin suppression and/or androgen suppression is desired. Gonadotropin suppression is achieved according to this invention by administration of a neurokinin-3 (NK-3) receptor antagonist. More in particular, this invention relates to a method of gonadotropin suppression, e.g., by lowering luteinizing hormone (LH) blood levels by administering to a mammal in need thereof, an effective amount of an NK-3 receptor antagonist. Concurrently or alternatively with gonadotropin suppression, this invention also relates to suppression of androgen production with NK-3 receptor antagonists. Suitable NK-3 receptor antagonists useful in this invention are represented by the compounds described herein.

BACKGROUND OF THE INVENTION:

Gonadotropins, including LH and follicle-stimulating hormone (FSH), are released by the pituitary gland and stimulate the production of steroid hormones by the gonads. Androgens, the principal one being testosterone, are secreted mainly by the testes and, to a lesser degree, by the adrenal cortex and ovary. In males, they are involved in the development and maintenance of secondary sexual characteristics and several physiological functions, such as normal reproduction, sexual performance ability, and skeleton and skeletal muscle growth and development during puberty. In females, they stimulate growth of pubic hair and probably libido, as well as acting as estrogen precursors. Antiandrogens are drugs that antagonize the effects of androgens. Antiandrogens are known to be useful in treating benign prostatic hyperplasia (BPH), androgen-dependent acne, and prostatic cancer. Korolkovas, A., Essentials Of Medicinal Chemistry, Second Edition, pp. 1009-1015 (1988).

Steroid hormones, including testosterone, not only play an important role in regulating growth, differentiation and function of organs such as the gonads, pituitary and sex organs, but, they are also involved in mediating BPH, and many cancers, including those of the prostate, e.g., metastatic prostatic carcinoma, breast, testicles and endometrium. H. Vanden Bossche, *J. Steroid Biochem. Molec. Biol.*, Vol. 43, No. 8, pp. 1003-1021 (1992).

BPH is a disease in which the prostate resumes growth late in life. Hormonal imbalance plays an important role among the etiologic factors of BPH (Sciarra et al.,

Antiandrogens: clinical applications, *J. Steroid Biochem. Molec. Biol.*, Vol. 37, pp. 349-362 (1990)). The impact of androgens on prostatic carcinoma is known, as is the treatment of prostate cancer by androgen deprivation, including androgen blockade and inhibition of androgen synthesis (Huggins et al., *Archs. Surg.*, Vol. 43, pp. 209-223 (1941)).

In addition, steroid hormones are widely used as contraceptives.

Antispermatic agents are male contraceptives that inhibit spermatogenesis, the process leading to mature spermatazoa. Drugs that interfere in this process include androgens and antiandrogens. Since the antiandrogenic effects of the compounds claimed herein are reversible, the compounds may be useful as a male contraceptive agent. Korolkovas, A., Essentials Of Medicinal Chemistry, Second Edition, pp. 1032 (1988).

Hyperandrogenism (excess production and secretion of androgens and precursors) is a common and sometimes serious endocrinopathy for women of reproductive age. The excess androgens and precursors originate from the adrenal glands and ovaries in various proportions and manifest in varying effects depending on the amount of excess androgen. Clinical manifestations range from hirsutism (excessive hair growth of male pattern, sometimes accompanied by acne) to virilization (clitorimegaly, temporal balding, deepening of voice, or enhanced musculature). Hyperandrogenism occurs as part of a wide spectrum of disease manifestations, including polycystic ovary syndrome (PCOS) which is a variable combination of hirsutism, infertility, obesity, insulin resistance and polycystic ovaries, the HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), and other manifestations of high intraovarian androgen concentrations (e.g., follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen-producing tumors (virilizing ovarian or adrenal tumors).

Current medical therapies for women are directed against the adrenals, the ovaries or the androgen receptor. Glucocorticoid therapy is directed against the adrenal glands but is limited, in some cases, by unwanted suppression of cortisol synthesis. GnRH therapy is directed against the ovaries, but is expensive, and its long-term effects are unknown. Further, therapy using oral contraceptives may be unsuitable because most contain progestins with androgenic activity.

Because the abnormal production of androgens is implicated in the pathways of many diseases and/or disorders for which there are no acceptable treatments, a need exists to find small molecules to inhibit the production of gonadotropins and/or

androgens in mammals for their treatment and/or prophylaxis. The current invention teaches that NK-3 receptor antagonists broadly, and the compounds described herein specifically, suppress gonadotropin production and/or androgen production/secretion, and therefore, are useful in the treatment and/or prophylaxis of diseases or disorders in which decreased levels of androgens are desired.

In men these diseases or disorders, include, but are not limited to, BPH, prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, androgen dependent acne, male pattern baldness and precocious puberty in boys. In addition, according to this invention, NK-3 receptor antagonists and the compounds herein would be useful as male contraceptives and to inhibit the sex drive in male sexual offenders.

In women, the above-mentioned syndromes manifest from excess androgen production/secretion. Therefore, administration of an NK-3 receptor antagonist according to this invention would be an effective treatment of those syndromes. In addition, administration of an NK-3 receptor antagonist according to this invention would be useful in the suppression of preovulatory LH surges in assisted reproductive technologies, and in treating or preventing endometriosis, estrogen-dependent (or positive) breast cancers, and uterine leiomyomas (fibroids).

SUMMARY OF THE INVENTION:

The present invention is to the novel use of antagonists of the NK-3 receptor to achieve gonadotropin and/or androgen suppression in mammals. According to this invention, NK-3 receptor antagonists are administered for the treatment and/or prophylaxis of diseases which are caused by abnormal levels of androgens, particularly testosterone. The compounds described herein by reference are particularly useful according to this invention.

DETAILED DESCRIPTION OF THE INVENTION:

Surprisingly, it has now been found that NK-3 receptor antagonists are effective in reversibly suppressing gonadotropin and/or androgen production/secretion, specifically the production of LH and/or testosterone in mammals. Suppression of gonadotropin production/secretion results in the suppression of androgen production/secretion. Thus, the instant invention is in a method of treatment and/or prophylaxis of disease states or disorders which are effected, or exacerbated by, elevated and/or abnormal levels of gonadotropins and/or androgens. Specifically, the invention relates to a method of suppressing gonadotropin and/or androgen blood levels by administering an effective amount of

an NK-3 receptor antagonist. The compounds defined herein exhibit the ability to suppress gonadotropin and/or androgen production, and in particular, are effective in reversibly lowering blood levels of LH and the androgen testosterone.

5 The term "androgen" is used herein to mean steroids that encourage the development of male sex characteristics and include the steroid derivatives of androstane including, testosterone, androstenedione, and analogs.

As used herein, a disease state or disorder characterized by "androgenic dependency" is a disease state which is exacerbated by, or caused by, insufficient, excessive, inappropriate or unregulated androgen production. Examples of such
10 diseases in men include, but are not limited to, BPH, metastatic prostatic carcinoma, testicular cancer, androgen dependent acne, male pattern baldness and precocious puberty in boys. Examples of such diseases in women include, but are not limited to, hyperandrogenism, hirsutism, virilization, POCS, HAIR-AN syndrome, ovarian hyperthecosis, follicular maturation arrest, atresia, anovulation, dysmenorrhea,
15 dysfunctional uterine bleeding, infertility, androgen-producing tumors.

As used herein, "gonadotropin suppression" refers to the reduction in the production or synthesis of one or more naturally occurring gonadotropins, including lutinizing hormone and follicle-stimulating hormone.

As used herein, "androgen inhibiting" refers to an effective amount of an
20 NK-3 receptor antagonist or other compound defined herein, which will cause a decrease in the *in vivo* levels of the androgen to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated androgen production. Without being bound to a particular theory of this invention, current findings
25 indicate that the antiandrogenic activity of the NK-3 receptor antagonists described herein involves a direct inhibition of testicular synthesis of testosterone and/or a suppression of LH release from the pituitary.

Compounds for use herein include the NK-3 receptor antagonists as described in, and made according to, WO 95/32948, published December 7, 1995, as
30 Farina et al.; WO 96/02509, published February 1, 1996, as Farina et al.; WO 97/19926, published June 5, 1997, as Giardina et al.; WO 97/21680, published June 19, 1997, as Giardina et al.; WO 98/52942, published November 26, 1998, as Giardina et al., WO 98/05640, published February 12, 1998, as Grugni et al., and EP0673928, published September 27, 1995, as Bichon et al., which are incorporated
35 herein by reference in their entirety.

Particularly preferred compounds for use herein are as follows:

((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide);

(S)-(-)-N-(α -Ethylbenzyl)-3-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy]-2-phenylquinoline-4-carboxamide;

(+)-(R)-3-[3-(4-Phenyl-4-N-methylacetamidopiperidin-1-yl)propyl]-3-(3,4-dichlorophenyl)-1-benzoylpiperidine;

5 (S)-(-)-N-(α -Ethylbenzyl)-3-(3-carboxy)propoxy-2-phenylquinoline-4-carboxamide; and

(S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide.

10 Methods for preparing the compounds described above as useful in this invention are described in WO 95/32948, published December 7, 1995, as Farina et al.; WO 96/02509, published February 1, 1996, as Farina et al.; WO 97/19926, published June 5, 1997, as Giardina et al.; WO 97/21680, published June 19, 1997, as Giardina et al.; WO 98/52942, published November 26, 1998, as Giardina et al., and WO 98/05640, published February 12, 1998, as Grugni et al., which methods are
15 incorporated herein by reference.

The present invention further provides a pharmaceutical composition comprising an NK-3 receptor antagonist or a compound described above, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

20 The present invention also provides the use of an NK-3 receptor antagonist or a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of diseases in which modified levels of androgens are desired, including, but not limited to, BPH, metastatic prostatic carcinoma, testicular cancer, androgen
25 dependent acne, male pattern baldness, precocious puberty in boys, hyperandrogenism, hirsutism, virilization, POCS, HAIR-AN syndrome, ovarian hyperthecosis, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility, androgen-producing tumors.

30 Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavoring agent, coloring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

35 Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

5 The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of
10 the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

15 The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or
20 pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier
25 suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if
30 desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for
35 example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or

non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional
5 flavoring or coloring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or
10 non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives.
15 Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via
20 the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the
25 sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilizing a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive
30 adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the
35 particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250,

300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

BIOLOGICAL DATA:

The antiandrogenic effects of the compounds useful herein are determined by the following summary which demonstrates reproductive organ and testosterone effects.

Once daily oral administration of ((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide) for 1 month to sexually mature male beagle dogs (12 - 16 months of age) produced decreases in the size and/or weight of testes and prostate. Histologic evaluation of these tissues revealed degeneration of the seminiferous epithelium of the testes with depletion of spermatogonia, spermatocytes and spermatids and diffuse atrophy of the prostate gland. The incidence and severity of these changes were dose-related with 1 of 3, 2 of 3, 2 of 3, 6 of 6 and 3 of 3 male dogs affected at doses of 0.3, 3, 30, 300 or 1000 mg/kg per day, respectively. The reversibility of these changes has also been demonstrated.

Once daily oral administration of ((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide) for 1 month to male rats or for 2 weeks to male mice had no effect on the weights and/or histologic appearance of the reproductive organs. The daily doses ranged from 0.1 to 1000 mg/kg per day.

The ((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide)-dependent changes in the testes and prostate of male dogs were associated with reductions in serum concentration of testosterone. Testosterone concentrations were reduced after either a single oral dose of 300 mg/kg (3 of 3 dogs) or 25 daily oral doses of 0.3 (1 of 3 dogs), 3 (2 of 3 dogs) or 300 mg/kg ((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide) (3 of 3 dogs). Serum testosterone was measured on blood samples obtained every 2 hours for 24 hours after the single dose and every 20 minutes for 4 hours beginning approximately 2 hours after the last of the 25 daily doses. The reductions in serum testosterone observed after one or 25 daily doses of 300 mg/kg ((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide) were reversible in all dogs (6 of 6) within one week after the cessation of dosing.

The growth and maintenance of the testes and prostate are androgen dependent. Consequently, the testicular degeneration and prostatic atrophy observed in dogs given ((S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide) appears to be associated with the reduced serum concentration of testosterone. Furthermore, because testosterone is produced in the testes (Leydig cells), the occurrence of testicular degeneration indicates that the reduction in serum testosterone is due to an inhibition of synthesis, and not to an enhanced elimination of circulating testosterone.

A single oral dose of 300 mg/kg (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide produced a rapid and marked decrease in serum concentration of testosterone in male dogs that lasted for at least 24 hours post-dose. This effect was reversible and was associated with a reduction in serum concentration of luteinizing hormone (LH). This dose of (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide also reduced the plasma concentration of androstenedione, but had no effect on plasma concentrations of estradiol or cortisol in male dogs. A single intravenous dose of 10 mg/kg (approximately 26 umoles/kg) (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide also reduced plasma concentration of testosterone in male dogs. The quinoline derivatives (S)-(-)-N-(α -Ethylbenzyl)-3-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy]-2-phenylquinoline-4-carboxamide and (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide, which possess NK-3 receptor antagonist activity, reduced plasma concentration of testosterone in male dogs when given intravenously at a dose of approximately 26 umoles/kg. A piperidine derivative possessing NK-3 receptor antagonist activity ((+)-(R)-3-[3-(4-Phenyl-4-N-methylacetamidopiperidin-1-yl)propyl]-3-(3,4-dichlorophenyl)-1-benzoylpiperidine) also reduced plasma testosterone of male dogs when given intravenously at a dose of approximately 26 umoles/kg. The single intravenous doses of (+)-(R)-3-[3-(4-Phenyl-4-N-methylacetamidopiperidin-1-yl)propyl]-3-(3,4-dichlorophenyl)-1-benzoylpiperidine and (S)-(-)-N-(α -Ethylbenzyl)-3-[3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy]-2-phenylquinoline-4-carboxamide that reduced plasma testosterone in male dogs had no effect on plasma estradiol concentration and did not lower plasma cortisol concentration.

Four daily oral doses ≥ 100 mg/kg (S)-(-)-N-(α -Ethylbenzyl)-3-(3-carboxy)propoxy-2-phenylquinoline-4-carboxamide or (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide reduced the plasma testosterone concentration of male rats when measured at 4 hours after the last dose. Four daily oral doses of 300 mg/kg (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-

phenylquinoline-4-carboxamide also reduced plasma LH concentration in male rats when measured at 4 hours after the last dose. Reductions in plasma testosterone also occurred in male rats following single oral doses of 30 to 1000 mg/kg (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide. Stimulation of testosterone production *in vivo* by a LH agonist (human chorionic gonadotropin) was not blocked by a single oral dose of 1000 mg/kg (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide in male rats.

In vitro studies utilizing primary cultures of Leydig cells isolated from the testes of dogs demonstrated that (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide and (+)-(R)-3-[3-(4-Phenyl-4-N-methylacetamidopiperidin-1-yl)propyl]-3-(3,4-dichlorophenyl)-1-benzoylpiperidine are capable of directly inhibiting testicular synthesis of testosterone in male dogs. This effect occurred at incubation concentrations between 10 and 100 μ M. Furthermore, using lysed dog Leydig cells, it was demonstrated that the inhibition of testosterone synthesis by (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide involves inhibition of the enzyme (CYP17A1) in the testosterone synthetic pathway. (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide did not inhibit testosterone synthesis in dog Leydig cells at the highest incubation concentration tested (100 μ M). Neither (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide nor (S)-(-)-N-(α -Ethylbenzyl)-3-(3-carboxy)propoxy-2-phenylquinoline-4-carboxamide inhibited testosterone synthesis in Leydig cells isolated from the testis of the rat at the highest incubation concentration tested (300 μ M). In contrast, (+)-(R)-3-[3-(4-Phenyl-4-N-methylacetamidopiperidin-1-yl)propyl]-3-(3,4-dichlorophenyl)-1-benzoylpiperidine, and (S)-(-)-N-(α -Ethylbenzyl)-3-[(4-methylpiperazin-1-yl)methyl]-2-phenylquinoline-4-carboxamide inhibited testosterone synthesis of isolated rat Leydig cells at incubation concentrations between 3 and 300 μ M.

Studies using isolated Leydig cells demonstrated that the NK-3 receptor antagonists (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide, (+)-(R)-3-[3-(4-Phenyl-4-N-methylacetamidopiperidin-1-yl)propyl]-3-(3,4-dichlorophenyl)-1-benzoylpiperidine, and (S)-(-)-N-(α -Ethylbenzyl)-3-[(4-methylpiperazin-1-yl)methyl]-2-phenylquinoline-4-carboxamide can directly inhibit testosterone synthesis in the testis. In contrast, the NK-3 receptor antagonist (S)-(-)-N-(α -Ethylbenzyl)-3-carboxymethoxy-2-phenylquinoline-4-carboxamide was not capable of inhibiting testosterone synthesis by Leydig cells *in vitro* or of blocking LH agonist-induced testosterone synthesis *in vivo*. However, this compound was capable of lowering both plasma LH and testosterone concentrations. Since

testosterone synthesis in males requires stimulation by LH, the antiandrogenic activity of this compound appears to be due to its selective suppression of LH release. Finally, the NK-3 receptor antagonist (S)-(-)-N-(α -Ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide produced its antiandrogenic activity both by
5 suppressing LH release and by directly inhibiting testosterone synthesis.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding
10 description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method for the treatment and/or prophylaxis of a disease in a mammal in need thereof, which disease is characterized by androgenic dependency,
5 comprising administering to such mammal an effective amount of a compound which inhibits the production of an androgen.
2. The method of claim 1 wherein the androgen is testosterone.
- 10 3. A method for suppressing testosterone production in a mammal comprising administering to such mammal an effective amount of a compound which inhibits the production of testosterone.
- 15 4. A method of suppressing the production of luteinizing hormone in a mammal comprising administering to such mammal an effective amount of a compound which inhibits the production of gonadotropin.
- 20 5. The method according to claims 1, 3 and 4 wherein the compound is a neurokinin-3 receptor antagonist.
- 25 6. The method according to claim 1, wherein the disease is selected from BPH, metastatic prostatic carcinoma, testicular cancer, androgen dependent acne, male pattern baldness, precocious puberty in boys, hyperandrogenism, hirsutism, virilization, PCOS, HAIR-AN syndrome, ovarian hyperthecosis, follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility, androgen-producing tumors.

ABSTRACT OF THE DISCLOSURE

The present invention is to the novel use of NK-3 receptor antagonist compounds for the treatment and/or prophylaxis of diseases which are caused by high or inappropriate levels of gonadotropins and/or androgens, particularly testosterone.

09/889904-01001

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"ANTI-ANDROGENS AND METHODS FOR TREATMENT"

the specification of which (check one)

☐ is attached hereto.

☒ was filed on **25 January 2000** as Serial No. **PCT/US00/01956**

and was amended on

(if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
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I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/117,059	25 January 1999

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status
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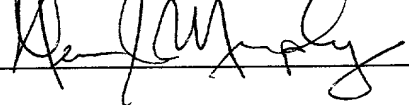
I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

Address all correspondence and telephone calls to **Nora Stein-Fernandez**, SmithKline Beecham Corporation, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is **610-270-5044**.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Dennis J. Murphy

Inventor's Signature: 

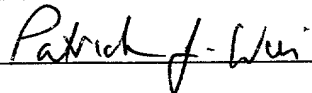
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T-130460-110569350

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My residence, post office address and citizenship are as stated below next to my name.

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Serial No.	Filing Date	Status
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Figure 1 consists of 12 subplots, each representing a different value of k from 0 to 11. Each subplot is a histogram showing the frequency of the number of non-zero elements in the rows of the matrix A_k . The x-axis for all plots is labeled 'Number of non-zero elements' and ranges from 0 to 100. The y-axis is labeled 'Frequency' and ranges from 0 to 10. The distributions are roughly bell-shaped and centered around 50-60 non-zero elements. The plots are arranged in a 6x2 grid. The first row contains plots for $k=0, 1, 2, 3$. The second row contains plots for $k=4, 5, 6, 7$. The third row contains plots for $k=8, 9, 10, 11$. The distributions appear to be relatively stable across different values of k .